

**Chronology of Events on CAMPTOSAR® (Irinotecan
Hydrochloride Trihydrate) IND 35,229; NDA 20-571**

| <u>DATE</u> | <u>EVENT</u> |
|------------------|---|
| August 3, 1990 | G.H. Besselar Associates submitted IND for CPT-11 on behalf of Kabushiki Kaisha Yakult Honsha. |
| August 6, 1990 | Letter from FDA acknowledging the August 6, 1990 submission and assigning IND number 35,229. |
| August 15, 1990 | G. H. Besselar letter submitting to FDA an additional copy of the IND. |
| October 22, 1990 | G.H. Besselar submits Response to FDA Request for Additional Protocol Amendment: Change in Protocol New Investigator. |
| March 4, 1991 | G.H. Besselar submits Protocol Amendment: Change in Protocol. |
| March 6, 1991 | G.H. Besselar submits Protocol Amendment: New Protocol. |
| March 18, 1991 | G.H. Besselar submits Other: Additional Secondary Investigators. |
| April 9, 1991 | G.H. Besselar submits Protocol Amendment: Change in Protocol. |
| August 1, 1991 | G.H. Besselar submits Change in Protocol (GHBA-393). |
| October 3, 1991 | G.H. Besselar submits Protocol Amendment: New Investigator. |
| October 9, 1991 | G.H. Besselar submits Annual Report. |
| October 16, 1991 | G.H. Besselar submits Protocol Amendment. |
| January 14, 1992 | G.H. Besselar submits Protocol Amendment: Change in Protocol. |
| October 1, 1992 | G.H. Besselar submits Annual Report. |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|--|
| November 4, 1992 | G.H. Besselar submits Response to FDA Request for Information. |
| November 30, 1992 | G.H. Besselar submits errors correct in the 1992 Annual Report. |
| December 8, 1992 | Theradex submits transfer of representative agent from G.H. Besselar to Theradex. |
| January 11, 1993 | Theradex submits Request for Compassionate Use. |
| January 28, 1993 | Theradex submits Request for Compassionate Use. |
| January 28, 1993 | Theradex submits Request for Compassionate Use. |
| February 1, 1993 | Theradex submits Prorovol: Cervical Cancer Phase II, M.D. Anderson, Protocol: Colorectal Cancer. |
| February 26, 1993 | Theradex submits Protocol Amendment: Cervical/Colorectal Cancer Phase II, Summary of IND Submission. |
| March 5, 1993 | Theradex submits Protocol: Cervical Cancer, Loyola Univ., Labels and certificates of analysis, Revised general investigational plan. |
| March 9, 1993 | Theradex submits Request for Compassionate Use. |
| March 17, 1993 | Theradex submits CMC update (Type I, Osaka plant). |
| March 23, 1993 | Theradex submits authorization for the FDA to release Theradex's name. |
| March 24, 1993 | Theradex submits Request for Compassionate Use. |
| March 26, 1993 | Theradex submits Request for Compassionate Use. |

| <u>DATE</u> | <u>EVENT</u> |
|--------------------|--|
| April 2, 1993 | Theradex submits Request for Compassionate Use. |
| April 8, 1993 | Theradex submits Request for Compassionate Use. |
| April 23, 1993 | Theradex submits Request for Compassionate Use. |
| April 29, 1993 | Theradex submits Protocol: Colorectal Cancer, Mayo Clinic. |
| May 6, 1993 | Theradex submits Request for Compassionate Use. |
| May 14, 1993 | Theradex submits IND Safety Report on the death of pt 19 at San Antonio. |
| June 3, 1993 | Theradex submits Request for Compassionate Use. |
| June 23, 1993 | Theradex submits Reply to FDA Comments. |
| August 4, 1993 | Theradex submits Request for Compassionate Use. |
| August 4, 1993 | Theradex submits Change in Protocol (MD Andersin/Amendment 5, CTTC/Amendment 3). |
| August 26, 1993 | Theradex submits Request for Compassionate Use. |
| September 21, 1993 | Theradex submits Request for Compassionate Use. |
| October 29, 1993 | Theradex submits Annual Report. |
| November 9, 1993 | Theradex submits Change in Protocol (Mayo Clinic/Amendment 3) |
| November 18, 1993 | Amendment No. 040, The Upjohn Company submits transfer of sponsorship along with all rights and obligations to the application from Yakult Honsha Co., Ltd., to The Upjohn Company, Kalamazoo, MI. |
| November 30, 1993 | Amendment No. 043 - Protocol Amendment. |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|--|
| December 14, 1993 | Letter from Division of Oncology and Pulmonary Drug Products, FDA, transfer of IND 35,229 accepted. |
| January 6, 1994 | Amendment No. 044 - Protocol Amendment - Compassionate Use Protocol. |
| February 18, 1994 | Amendment No. 045 - Protocol Amendment - Special Exception Protocol. |
| March 2, 1994 | Amendment No. 046 - Protocol Amendment. |
| March 25, 1994 | Amendment No. 047 - New Protocol M/6475/0006. |
| March 31, 1994 | Amendment No. 048 - New Investigator for Protocol M/6475/0006. |
| April 11, 1994 | Amendment No. 049 - TUC requests meeting with FDA to discuss development plans |
| April 21, 1994 | Amendment No. 050 - Teleconference (4/5/94) follow-up. |
| April 26, 1994 | Amendment No. 051 - Special Exception Protocol CPT-11/39424. |
| May 3, 1994 | Amendment No. 052 - Protocol Amendment. |
| May 18, 1994 | Amendment No. 053 - Protocol Amendment. |
| May 20, 1994 | Amendment No. 054 - Special Exception Protocol. |
| June 2, 1994 | Amendment No. 055 - Protocol Amendment |
| June 2, 1994 | Amendment No. 056 - Request meeting to discuss the potential for filing a NDA for the use of irinotecan to treat patients with colorectal carcinoma. |
| June 7, 1994 | Amendment No. 057 - Protocol Amendment. |
| June 9, 1994 | Amendment No. 058 - 10 day written report. |
| June 23, 1994 | Amendment No. 059 - Special Exception Protocol. |

| <u>DATE</u> | <u>EVENT</u> |
|--------------------|---|
| June 23, 1994 | Amendment No. 060 - Clinical Information - Follow-up to Amendment No. 058, 10 day written report. |
| July 5, 1994 | Amendment No. 061 - The Upjohn Company added as a manufacturing site for the drug product. |
| July 14, 1994 | Amendment No. 062 - Protocol Amendment. |
| July 21, 1994 | Amendment No. 063 - Change in Protocol. |
| July 22, 1994 | Amendment No. 064 - Requests telephone to discuss proposed toxicity program. |
| July 26, 1994 | Amendment No. 065 - Additional documents for the August 3 meeting with FDA. |
| August 1, 1994 | Amendment No. 066 - Item 7. Chemistry, B. Drug Product. |
| August 3, 1994 | Meeting with Division of Oncology and Pulmonary Drug Products to review clinical development plan leading to NDA submission. Minutes of the meeting submitted to IND in Amendment No. 071, October 7, 1994. |
| August 11, 1994 | Amendment No. 067 - 10 day Safety Report. |
| August 18, 1994 | Amendment No. 068 - Information Amendment. |
| August 22, 1994 | Amendment No. 069 - Information Amendment. |
| September 12, 1994 | Amendment No. 070 - Protocol Amendment. |
| October 7, 1994 | Amendment No. 071 - Information Amendment and minutes of 8/3/94 FDA meeting. |
| October 10, 1994 | Amendment No. 072 - Annual Report No. 4. |
| October 18, 1994 | Amendment No. 073 - Protocol Amendment. |
| October 26, 1994 | Amendment No. 074 - Protocol Amendment. |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|---|
| November 11, 1994 | Amendment No. 075 - Information Amendment. |
| November 17, 1994 | Amendment No. 076 - Protocol Amendment. |
| November 28, 1994 | Amendment No. 077 - 10 day Written Safety Report. |
| December 1, 1994 | Amendment No. 078 - Information Amendment. |
| December 2, 1994 | Amendment No. 079 - Proposed trademark submitted: CAMPTOSAR® Sterile Solution (irinotecan hydrochloride sterile solution). |
| December 5, 1994 | Amendment No. 080 - Information Amendment. |
| December 19, 1994 | Amendment No. 081 - Submission of Clinical Benefit Report in response to commitment made at August 3, 1994 FDA meeting. |
| December 22, 1994 | Amendment No. 082 - Protocol Amendment. |
| January 9, 1995 | Amendment No. 083 - Protocol Amendment. |
| January 11, 1995 | Letter to James Hamilton, Office of Compliance, FDA, requesting approval to defective clinical supplies. |
| January 27, 1995 | Amendment No. 084 - Protocol Amendment. |
| January 30, 1995 | Facsimile sent from Upjohn to Medical Reviewer with proposal for provision of case report forms (CRFs) for foreign studies to be included in the NDA. Several interchanges between sponsor and FDA. |
| February 13, 1995 | Telephone call from CSO relaying the following resolution on foreign CRFs to be included in the NDA: "The sponsor does not need to include CRFs from foreign phase I studies in the NDA. However, the sponsor should be prepared to submit CRFs for patients who died and |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|--|
| | experienced serious adverse medical events in phase II colorectal studies conducted in France and Japan." |
| February 16, 1995 | Amendment No. 085 - Protocol Amendment. |
| February 20, 1995 | Amendment No. 086 - Protocol Amendment. |
| February 22, 1995 | Amendment No. 087 - Information Amendment, Additional Data for 3/10/95 FDA meeting. |
| February 28, 1995 | Amendment No. 088 - Protocol Amendment. |
| March 6, 1995 | Amendment No. 089 - Information Amendment: Aseptic Processing. |
| March 10, 1995 | Meeting with Division of Oncology and Pulmonary Drug Products to review clinical benefit data; review of U.S. clinical trial experience (tumor responses, toxicity, and management of late diarrhea); filing proposal for treatment of previously treated colorectal cancer. Minutes of the meeting submitted to IND in Amendment No. 093, April 14, 1995. |
| March 14, 1995 | Amendment No. 090 - Protocol Amendment. |
| March 14, 1995 | Amendment No. 091 - Protocol Amendment. |
| April 4, 1995 | Amendment No. 092 - Protocol Amendment. |
| April 14, 1995 | Amendment No. 093 - Protocol Amendment. |
| April 26, 1995 | Amendment No. 094 - Protocol Amendment. |
| May 16, 1995 | Amendment No. 095 - General correspondence. |
| May 18, 1995 | Amendment No. 096 - Protocol Amendment. |
| May 22, 1995 | Amendment No. 097 - IND Safety Report - 10-day Written Report. |

| <u>DATE</u> | <u>EVENT</u> |
|-----------------|---|
| May 25, 1995 | Amendment No. 098 - General correspondence: Request for pre-NDA meeting. |
| June 6, 1995 | Amendment No. 099 - General correspondence: Additional copies of Pre-NDA Meeting Request Package. |
| June 12, 1995 | Amendment No. 100 - General Correspondence: Draft Protocol for Review. |
| June 16, 1995 | Amendment No. 101 - Protocol Amendment. |
| June 19, 1995 | Amendment No. 102 - Information Amendment. |
| July 6, 1995 | Amendment No. 103 - General Correspondence: Response to FDA Request for Information (comments on proposed analysis plan). |
| July 20, 1995 | Amendment No. 104 - General Correspondence: Request for C,M&C pre-NDA Meeting. |
| July 25, 1995 | Amendment No. 105 - Protocol Amendment. |
| August 4, 1995 | Amendment No. 106 - Safety Report: Follow-up Written Report. |
| August 7, 1995 | Amendment No. 107 - General correspondence: Reply to Comments on Draft Protocol. |
| August 10, 1995 | Amendment No. 108 - General correspondence: Package for CANDAs/Protocol 0038 Statistical Plan Mtg. |
| August 11, 1995 | Amendment No. 109 - New Protocol. |
| August 16, 1995 | Correspondence: Desk copy of Protocols for Medical Officer. |
| August 28, 1995 | Amendment No. 110 - Information Amendment. |
| August 28, 1995 | Amendment No. 111 - Protocol Amendment. |

| <u>DATE</u> | <u>EVENT</u> |
|--------------------|---|
| August 29, 1995 | CANDA meeting. |
| September 5, 1995 | Amendment No. 112 - Addendum to Request for pre-NDA Meeting; Revised Agenda. |
| September 13, 1995 | Amendment No. 113 - Overheads for pre-NDA Meeting. |
| September 15, 1995 | Amendment No. 114 - General correspondence: Response to FDA Request for Information - Clinical. |
| September 18, 1995 | Amendment No. 115 - IND Safety Report: 10-day Written Report. |
| September 29, 1995 | Amendment No. 116 - General Correspondence: CM&C Information - Teleconference report. |
| October 2, 1995 | Amendment No. 117 - General Correspondence: Minutes of August 29, 1995 CANDA meeting. |
| October 4, 1995 | Amendment No. 118 - Protocol Amendment. |
| October 4, 1995 | Pre-NDA Meeting (all items except CM&C). The proposal to submit the FDA under the accelerated approval regulations (21 CFR § 314.510, Subpart H) was accepted. Design of the confirmatory phase IV trial was tentatively agreed upon; design to be finalized and submitted by early 1996. |
| October 11, 1995 | Amendment No. 119 - General correspondence: Minutes of 9/6/95 CMC Pre-NDA Meeting. |
| October 23, 1995 | Amendment No. 120 - Protocol Amendment. |
| October 30, 1995 | Amendment No. 121 - Annual Report. |
| November 6, 1995 | Amendment No. 122 - General Correspondence - Minutes of October 4, 1995, Pre-NDA Meeting. |
| November 8, 1995 | Amendment No. 123 - Safety Report. |
| November 10, 1995 | Amendment No. 124 - New Investigators. |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|--|
| November 21, 1995 | Amendment No. 125 - Protocol Amendment. |
| November 29, 1995 | Amendment No. 126 - Safety Report. |
| December 1, 1995 | Amendment No. 127 - Safety Report. |
| December 8, 1995 | Amendment No. 128 - Safety Report. |
| December 13, 1995 | Amendment No. 129 - Change in Protocol. |
| December 14, 1995 | Amendment No. 130 - General Correspondence. |
| December 12, 1995 | Amendment No. 131 - New Protocol. |
| December 28, 1995 | NDA filed with and logged in to FDA. |
| December 28, 1995 | Letter sent to Division of Information Systems Design (HFD-70) with listing of CANDAs equipment. |
| January 3, 1996 | Letter sent to Division of Information Systems Design (HFD-70) updating listing of CANDAs equipment with information regarding the laptop computers for the medical reviewers. |
| January 11, 1996 | Leslie Vaccari (CSO) called and requested immediate installation of the CANDAs hardware (scheduled installation of 1/8/96 cancelled by FDA closure from 1/8 through 1/10 due to weather). CANDAs equipment delivered same day by A.A. Khan and J.P. Maile. SAS data sets were hand delivered by R.E. Gibson. |
| January 11, 1996 | Leslie Vaccari informed MAB that page 5/1/32 was missing from the reviewer copy. Replacement page was faxed. |
| January 16, 1996 | Fax from Leslie Vaccari thanking P&U for 1/11/96 CANDAs installation. |
| January 16, 1996 | Fax from H.J. DeKoning Gans to FDA. Requested feedback on proposed cut off date (12/31/95) and content of NDA Safety Update. |

| <u>DATE</u> | <u>EVENT</u> |
|------------------|---|
| January 17, 1996 | Telephone request from Leslie Vaccari to D.C. Beuving. Requested: immediate CANDAs training for medical reviewers; location of specific data within NDA; investigator information on behalf of FDA Division of Scientific Investigations. |
| January 18, 1996 | FDA fax responding to P&U fax of 1/16/96. FDA requests that the safety information provided be consistent with the ISS content submitted in NDA 20-571. |
| January 18, 1996 | A.M. Holt and A.A. Khan provide CANDA training to FDA medical reviewers, Drs. Murgo and Chico. A.M. Holt delivered investigator information requested during 1/17/96 telephone conversation between D.C. Beuving and Leslie Vaccari. Medical reviewers forwarded request for information (summarized in contact report from A.M. Holt dated 1/22/96). |
| January 19, 1996 | Fax from D.C. Beuving to Leslie Vaccari. Provided response to location of patient data requested by Dr. Murgo during 1/17/96 telephone conversation between D.C. Beuving and Leslie Vacari. |
| January 22, 1996 | FDA acknowledgement letter for the NDA (dated 1/22/96). Confirms date of FDA receipt of the application as 12/28/95. Indicates that unless notified to the contrary, the application will be filed in 60 days (calculated as 2/27/96). |
| January 22, 1996 | Dr. Turner (Scientific Investigations) called M.A. Baumgartner to request investigator information and protocol information from pivotal trials. |
| January 23, 1996 | Replacement battery for Dr. Murgo's laptop shipped via overnight mail. |
| January 25, 1996 | Leslie Vaccari called M.A. Baumgartner to request information regarding addresses and DMFs for the Japanese manufacturer and subcontractors for the drug substance. This information is needed to |

DATE

EVENT

support scheduling of the PAI. During the conversation Leslie Vaccari reported that the replacement battery mailed 1/23 is also defective after charging. She requested a second battery.

January 26, 1996 Fax from M.A. Baumgartner to Leslie Vaccari provides requested facility addresses for Yukult Honsha, Sato and Shiratori. Also, addressed DMF issue and provided primary contact at Yukult for DMF 8553.

January 26, 1996 Second replacement battery mailed to Leslie Vaccari for 1/29/96 delivery.

January 29, 1996 Leslie Vaccari called to say that, regarding the EA, it may delete certain format items under the recent guidance to industry (announced in 1/11/96 FR). She suggested that "withdrawal" can be accomplished by superseding via submission of modified EA through the Amendment mechanism.

January 29, 1996 Fax received on EA issue.

January 30, 1996 Submitted response to reviewer questions on the CANDA (from A.M. Holt at the 1/18/96 training session). Submitted as Amendment 001 to the NDA.

January 31, 1996 Submitted response to Dr. Turner's request for protocols, CI information and volume 1.1.

February 1, 1996 Dr. Turner called and identified the CIs to be audited; to request specific CRFs and ADR listings for the CIs identified.

February 6, 1996 Submitted response to Dr. Turner's 2/1/96 request.

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|---|
| February 12, 1996 | Telephone contact with Leslie Vaccari. 45 day meeting will be held today. The review team is planning on a June ODAC with an action letter shortly thereafter. Would like revised EA submitted ASAP (prior to 60-day milestone). |
| February 13, 1996 | Telephone contact with Leslie Vaccari. No major deficiencies noted at the 45-day meeting. Planning on a June ODAC. Action letter could come as early as 6/28/96. |
| February 13, 1996 | Dr. Chico contacted A.A. Khan to resolve some CANDAs export problems. A telephone conference will be needed to resolve. Message left on Chico's voice mail suggesting call on February 14, 1996. |
| February 14, 1996 | Mailed Amendment 002 to the NDA which contained the revised EA and two corrected pages for Item 3. Corrected CMC pages sent to Detroit office for inclusion in field copy. |
| February 14, 1996 | Contacted Leslie Vaccari to facilitate scheduling a teleconference with Dr. Chico. |
| February 16, 1996 | Fax from Leslie Vaccari to MAB. Comments from Biopharm reviewer. Request for PK data availability in an electronic format. |
| February 20, 1996 | Telephone call with Leslie Vaccari regarding the desire of the biopharm reviewer to get the electronic information detailed in the fax of 2/16. Annette Holt spoke with Dr. Chico regarding the database issues. MAB followed up and offered assistance with respect to producing custom datasets. |

| <u>DATE</u> | <u>EVENT</u> |
|-------------------|--|
| February 21, 1996 | Larry Schaaf (Clin. PK) spoke with Dr. Williams. It was agreed to send WP 5.2 files immediately for the Item 6 summary and to provide data sets for the "pivotal" phase II studies. Larry Schaaf to call Dr. Williams with estimates of time frame for data sets for Phase II and with results of assessment of feasibility for data builds for the Phase I studies conducted by Yakult/ Daiichi/Besselar. |
| February 22, 1996 | MAB spoke with Leslie Vaccari regarding submission of disks. She requested two sets of disks be formally submitted to the application as general correspondence (PK and archival jackets). This and all future letters should be submitted in NDA jackets to expedite processing in the document control room. Letter/disks sent by overnight mail. |
| February 22, 1996 | M.A. Clasby met with FDA inspector Tom Hillary regarding other issues. During the conversation the issue of the CPT-11 PAI was raised. He has tentatively agreed to conduct the PAI starting April 15. |
| February 23, 1996 | A telecon was held between Schaaf, Baumgartner and P&U consultants Grasela and Fieldler-Kelly. Reached agreement on additional deliverables. |
| February 27, 1996 | Faxed summary of 2/23/97 teleconference to FDA Project Manager, Leslie Vaccari. |
| February 28, 1996 | Data sets used for structural models plus control streams provided to Dr. Williams by Fieldler-Kelly. |
| March 1, 1996 | Remainder of Phase II data sets sent to Williams by Fieldler-Kelly. |
| March 7, 1996 | Data sets for Phase I studies 0027 and DM111 sent to Williams. |

DATE

EVENT

| | |
|----------------|--|
| March 7, 1996 | Telephone conversation between Dr. Williams and Larry Schaaf. Updated Dr. Williams regarding status of response. |
| March 8, 1996 | Telephone conversation between MAB and Leslie Vaccari. Review continues to proceed smoothly. Modified EA was hand delivered to HFD-357 (Nancy Sager's group). The Microbiology review is back; no deficiencies noted. Trademark review will occur at the end of this month. Leslie OK'd upgrade of the export software for the CANDAs. A. Khan will install 3/11/96. |
| March 8, 1996 | From M.A. Clasby from interaction with inspector Tim Hillary: the CPT-11 pre-approval inspection in Kalamazoo is now scheduled to start on Wednesday, April 17th rather than Monday, April 15th. The change has been made so that the PAI for Remifentanyl can occur on the 15th and 16th of April. |
| March 22, 1996 | General Correspondence - NDA Safety Update. |
| April 3, 1996 | Amendment 004 - Response to Request for Information - Additional use report forms. |
| April 4, 1996 | Desk copies of updated SAS Datasets (safety and efficacy) sent to Leslie Vaccari. It was agreed with Leslie that Archive copy would follow. |
| April 5, 1996 | PAI scheduled for Kalamazoo changed to begin 4/29/96-4/30/96 per contact between Martha Clasby and Tim Hillary. |
| April 15, 1996 | Amendment 005 - Updated Summary of Efficacy. |
| April 18, 1996 | PAI finished at Sato with 483 issued with 2 minor observations. Approval will be recommended. Shiratori will be inspected the 19th with Yakult finished up by the 26th. |

| <u>DATE</u> | <u>EVENT</u> |
|----------------|--|
| April 18, 1996 | The PAI scheduled for 29th and 30th in Kalamazoo will need to be rescheduled at FDA's request (schedule conflict with FDA Inspector, Tim Hillary) for May 7. |
| May 8, 1996 | General Correspondence - Response to Information Request. |
| May 16, 1996 | Amendment 006 - Response to FDA Request for Information - Environmental Assessment. |
| May 16, 1996 | Oncologic Drugs Advisory Committee Brochure - for June 13, 1996 meeting. |
| May 16, 1996 | Sent to desk copies of Oncologic Division Advisory Committee Brochure and copy of revised Environmental Assessment to Ms. Leslie Vaccari as requested during 5/16/96 telephone conversation. |
| May 16, 1996 | Correction to Oncologic Drugs Advisory Committee Brochure. Correction of Protocol. |
| May 21, 1996 | Response to telephone facsimile transmission of May 17, 1996 requesting additional information regarding stability data. |
| May 21, 1996 | General correspondence - response to request for information. |
| May 28, 1996 | Amendment 007 - Correction to Clinical/Statistical Information (Amendment 003). Page 57 of Volume 1, section 8, "Discontinuations Due to Death and/or On-Study Deaths". |
| May 29, 1996 | Amendment 008 - Chemistry, Manufacturing, and Control section - labeling. Copies of proofs for vials, cartons, and blister packs for the product. |
| May 29, 1996 | Desk Copies of Amendment 008 providing proofs of labels for vials, cartons and blister packs. Sample of blister pack with an empty, uncapped vial enclosed. |

| <u>DATE</u> | <u>EVENT</u> |
|---------------|--|
| May 30, 1996 | Amendment 009 - Phase 4 Study - Prot. M/6475/0038 mentioned in letter. |
| May 31, 1996 | Correction to Oncologic Drugs Advisory Committee Brochure. Previous package erroneously included the outdated statistical section. |
| June 4, 1996 | Amendment 010 - Response to FDA Request for Information - Environmental Assessment - Revised EA information: Format items 9 and 10. |
| June 5, 1996 | Received missing pages from the background material submitted by the Oncology Division. Also included was a draft of the questions prepared by the division for TUC. |
| June 6, 1996 | General Correspondence - Response to FDA Request for Information - Postmarketing Study Commitments. Prot. M/6475/0038, M/6475/0037, M/6475/0033, M/6475/0062 mentioned in response letter. |
| June 6, 1996 | General correspondence - Response to FDA Request for Information (May 31, 1996 facsimile request) - Microbiologist's Request for Postmarketing Commitments. |
| June 7, 1996 | Amendment 011 - Response to FDA Request for Information. (Per fax of 6/4/96). |
| June 7, 1996 | Oncologic Drugs Advisory Committee (ODAC) - Providing a list of consultants who will be at the 6/13/96 ODAC Meeting as requested by FDA. |
| June 10, 1996 | Amendment 012 - Response to FDA Request for information related to chemistry review. |
| June 10, 1996 | General Correspondence - Request for Teleconference. Letter to Dr. Delap re questions which will be presented at the ODAC. |

| <u>DATE</u> | <u>EVENT</u> |
|---------------|--|
| June 11, 1996 | Amendment 013 - Response to FDA Requested Changes to the Product Labeling. In response to FDA's 5/31, 6/3, 6/7 and 6/10 facsimiles. |
| June 11, 1996 | Proposed news release pending a favorable recommendation at the Oncologic Drugs Advisory Committee Meeting. Also attached is the current draft package insert. |
| June 12, 1996 | Letter to Tracy Acker requesting comments of proposed news release with background information pending favorable recommendation for approval by the ODAC. |
| June 12, 1996 | MACMIS ID #4364 - Letter to K.J. Day providing comments regarding proposed press release in the event of a favorable recommendation for approval by the ODAC. |
| June 13, 1996 | MACMIS ID #4364 - Response to proposed press release following the ODAC meeting on 6/13/96. |
| June 14, 1996 | FDA letter giving approval of NDA 20-571 providing for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed following 5-FU-based therapy. |
| June 14, 1996 | General Correspondence - Response to FDA Request. |